RESPONSE OF HUMAN SWEAT GLANDS TO LOCAL HEATING*

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The responsiveness of sweat glands to locally applied heat was first reported by Saito (1) who observed sweating from the denervated foot-pad of the cat upon warming of the part, as well as localized thermal sweating in normal human skin. This response of human eccrine sweat glands was further characterized by Randall (2), Janowitz and Grossman (3) and Benjamin (4). The latter author studied the conditions of local temperature and environmental temperature and humidity which determine the response. In the several cited reports, the effects of a variety of locally applied blocking drugs were observed: reduction in the degree, or elevation in the threshold, of the response, but not its abolition, was produced with procaine, with atropine and hexamethonium. These findings, and the continued responsiveness of the glands after denervation (3), suggested that the thermal effect was, at least in part, independent of the innervation of the glands, whether this might be acting through a central or an axone reflex mechanism.

Our immediate interest in this response to local heating arose from speculation on the physiological significance of axone reflex sweating, which Kuno (5) had suggested might play a role in local response to warming of the skin. With this in mind, and despite the suggestion from earlier work that the direct effect of heat on the sweat glands is independent of innervation, we sought to test whether local heating of the skin might under any circumstances elicit sweating by way of an axone reflex. This would be initially suggested by the appearance of sweating outside the heated area. Part 1 of the results indicate that there is no evidence for an axone reflex response to local heating. The opportunity was afforded, however, to elucidate further the mechanism of response of the sweat glands to direct heating (parts 2 and 3).

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METHODS

In 7 male and 2 female Caucasian subjects, and 2 male Negro subjects, 20 to 40 years of age, the skin of the volar surface of the forearm was heated by either or both of two metal discs, each 20 mm in diameter, set flush in a solid plastic plate which held them at a fixed distance between centers of 75 mm. Each disc was the lower end of a cylinder through which warmed water of known temperature could be continuously circulated by a pump from a thermostatically controlled reservoir. In many experiments, a thermocouple attached to the disc was used to measure skin temperature. The temperature drop from reservoir to disc was then found to be constant with fixed rate of circulation, so that the bath temperature could be taken as a rough estimate of the disc temperature when the latter was not directly measured. The plastic plate with the heated discs was held on the skin with constant, firm pressure for approximately 2 to 10 minutes. Sweating was detected by Randall's (6) iodine-starch paper method. At least one 60 to 120 second sweat print was made before heating was started, as a control on background sweating. Just prior to application of the heater, a paper was laid on the skin and left in place during the heating for about 2 minutes. The heater was then rapidly raised, the sweat print removed, a new paper put in place and the heater immediately replaced in its original location on the skin. This procedure was repeated throughout the entire period of heating; serial prints were made for several minutes thereafter when indicated.

The cholinesterase inhibitor, paraoxon (diethyl 4-nitrophenyl phosphate),† dissolved in sterile 0.9% NaCl in a concentration of 1.45×10^{-4} M, was injected intradermally, when indicated, in volumes of 0.02 to 0.05 ml, into the area to be heated. The same procedure was used in some experiments with procaine hydrochloride 20 mg per ml, alone or in combination with 1.45×10^{-4} M paraoxon. In most experiments with procaine and in all with atropine, the agent was introduced into the skin by iontophoresis. To accomplish this a felt disc 20 mm in diameter was wet with a solution of the agent in 0.9% NaCl and held to the skin by a brass disc of the same size, to which was attached a handle of plastic tubing. This disc served as the anode in a battery operated circuit of which the cathode was a brass plate held in the hand or strapped to the opposite wrist; the current was indicated directly by a milliammeter

† We are indebted to Dr. Richard J. Magee of the American Cyanamid Co. for the paraoxon used in these experiments.

and could be adjusted by a voltage divider. Control of this procedure was accomplished by application of 0.9% NaCl by iontophoresis with the same current and duration, either separately or simultaneously with the test agent. The control area was heated in the same manner as the test area, separately or simultaneously.

Observations were made in a room whose temperature could be adjusted and held constant to within about 1° C. The relative humidity could not be adjusted; it was in the range of 20 to 65%.

RESULTS

Characteristics of the thermal response

In all essential respects, the local response to heating, illustrated in Fig. 1A, was as described by Randall (2). Sweating was localized entirely to the area which was heated, with the occasional exception of some spots a few millimeters outside the area. This strict limitation of the response occurred even when local temperature was raised to a definitely painful level (44–46° C) and when ambient temperature was just below the threshold for producing generalized sweating (27–28° C). These results in 32 trials on 4 subjects also confirmed Benjamin's (4) demonstration that the sweating occurs when epidermal temperatures reach 39°–42° C. at environmental temperature of 29° C., varying with relative humidity.

Effect of local anesthesia

In six experiments, procaine was introduced by iontophoresis into the area to be heated. The felt pad was soaked with a solution of 100, 200 or 400 mg per ml of the agent, and current of 2 milliamp. (4 milliamp. in one case) was allowed to flow for 10 minutes; superficial anesthesia occurred in all cases. At a concentration of 100 mg per ml, procaine did not alter sweating, but concentrations of 200 or 400 mg per ml produced substantial diminution of sweating in response to heating; this was especially evident during the first minutes of heating when nearly complete inhibition of sweating occurred, but the difference between responses in the anesthetized and control areas rapidly diminished thereafter. Similar diminution of sweating was observed in 8 experiments when procaine, 20 mg per ml, was injected intradermally.

Effects of paraoxon and atropine

In three experiments, 0.02 to 0.05 ml of 1.45 $\times$ 10^{-4} M paraoxon was injected intradermally

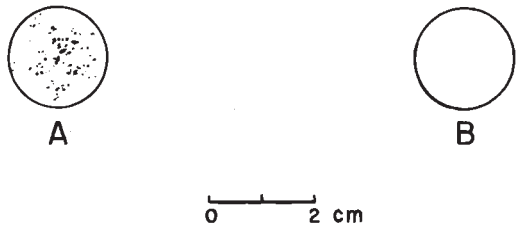

FIG. 1. Sweat print of forearm taken after 3½ minutes of heating at approximately 48° C.; ambient temperature was 29° C., relative humidity 35%. At A, 0.9% NaCl, and at B, atropine (1 mg per ml in 0.9% NaCl) had been introduced by iontophoresis at 2 milliamp. for 10 minutes; heating was started 5 minutes thereafter.

8 to 15 minutes prior to the local heating. This interval allowed the development of local sweating in response to endogenous acetylcholine accumulated in the presence of the cholinesterase inhibitor, as previously described (7). Under these conditions, maximal heating yielded intense local sweating, greater in magnitude and duration than the controls. After heating was stopped, some diffuse sweating was observed for several minutes outside the central area. Injection of a combination of paraoxon and procaine, at final concentrations of 1.45 $\times$ 10^{-4} M and 20 mg per ml respectively, to determine the effect of local anesthesia on the augmentation produced by paraoxon, yielded inconclusive results in 8 experiments; reduction and increase in the paraoxon effect were equally observed.

The suggestion arising from the augmenting action of paraoxon that acetylcholine might be involved in the local response to heat was further tested by observing the effect of atropine, locally administered by iontophoresis. In 4 experiments, atropine was used in a concentration of 0.4 mg per ml, and in 12 trials, 1.0 mg per ml. Current of 1 to 5 milliamp. was allowed to pass for from 4 to 10 minutes. In 4 trials, a marked diminution in the sweating response was observed; in the remaining 12, complete inhibition occurred (Fig. 1). In these experiments, the control in each case consisted in simultaneous heating of the second area after iontophoresis of unbuffered saline or of phosphate buffer at pH 4 (the same pH as the atropine solution), or with no iontophoresis at all; the specific nature of the control had no influence on the results. In 3 of the experiments, atropine (1 mg per ml), introduced into the skin by a current of 2 to 4 milliamp. for 10 minutes, having produced

complete block of the thermal sweating, reduced by a considerable amount the local and axone reflex response to the intradermal injection of 0.05 ml of 1:100,000 acetylcholine; this was tested after the skin had been allowed to cool. Two additional experiments were performed in which the amount of atropine introduced into the skin (1 mg per ml, 1 milliamp., 5 minutes) was insufficient to block completely the local thermal response. Generalized reflex sweating induced by heating the subject's back with a heat lamp was entirely absent in the atropine-treated area.

DISCUSSION

Even under the conditions of maximal cutaneous heating and environmental temperature just below threshold for reflex sweating, no definite evidence was obtained to implicate an axone reflex in the local thermal response. An axone reflex response would have been manifested by the appearance of sweating in a region of skin surrounding the heated area; but in general the sweating was localized to this area. This finding is quite the same as reported by earlier workers (2, 3) and speaks against Kuno's (5) suggestion on the possible role of axone reflex sweating. Conceivably, such a mechanism may play a role when environmental temperature is higher and generalized reflex sweating is occurring. But, under these circumstances the demonstration of an axone reflex would be most difficult, if at all possible, with present technics.

Our results on the effect of local anesthesia are consistent with previous results (2, 4) indicating that this procedure reduces but does not abolish the local thermal sweat response; the qualification must be made that in our experiments it was not possible adequately to control the duration of effective anesthesia. The observations of Janowitz and Grossman (3) on the thermal response in sympathetically denervated skin further support the thesis that the response is at least in part independent of the innervation of the sweat glands.

Two sets of findings suggest that the sweat response involves the mediation of acetylcholine. The augmenting action of paraoxon is compatible with this concept, although this effect might result only from simple addition of the action of locally accumulated acetylcholine and a quite separate thermally responsive mechanism. Stronger support for the idea of a cholinergic mechanism stems from the ability of atropine to block completely the thermal response. The required local concentration of atropine is greater than that necessary to block reflex sweating; this may explain Randall's (2) failure to observe such a block. Of course, atropine may be producing its effect through some mechanism other than block of acetylcholine; the present experimental approach can neither confirm nor rule out this possibility. What might be the nature of this non-neural cholinergic mechanism is unclear.

SUMMARY

The local response of human sweat glands to direct heating does not appear to involve an axone reflex. The response is reduced, but not abolished by local anesthesia with procaine, and is thus apparently not dependent upon functional integrity of the sudomotor innervation. It is augmented by a cholinesterase inhibitor, paraoxon (diethyl 4-nitrophenyl phosphate), and inhibited by atropine; these observations suggest that acetylcholine is involved in mediation of the response.

REFERENCES

1. SAITO, K.: Local sweating on heated area of skin in man. J. Oriental Med., **13:** 53, 1930 (cited by Kuno (5), p. 284).
2. RANDALL, W. C.: Local sweat gland activity due to direct effects of radiant heat. Amer. J. Physiol., **150:** 365, 1947.
3. JANOWITZ, H. D. AND GROSSMAN, M. I.: The response of the sweat glands to some locally acting agents in human subjects. J. Invest. Derm., **14:** 453, 1950.
4. BENJAMIN, F. B.: Sweating response to local heat application. J. Appl. Physiol., **5:** 594, 1953.
5. KUNO, Y.: Human Perspiration, p. 291. Springfield (Ill.), Charles C Thomas, 1956.
6. RANDALL, W. C.: Quantitation and regional distribution of sweat glands in man. J. Clin. Invest., **25:** 761, 1946.
7. MCLAUGHLIN, J. T. AND SONNENSCHEIN, R. R.: Action of paraoxon (diethyl 4-nitrophenyl phosphate) on human sweat glands and the sympathetic axone reflex. Acta Pharmacol. (Kobenhavn), **17:** 7, 1960.